



Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

**Bayer HealthCare Comment on FDA draft Guidance on Drug
Substance – Chemistry, Manufacturing, and Controls Information.
Docket No. 2003 D-0571, CDER 200389; January 2004**

June 2, 2004

Bayer HealthCare AG
51368 Leverkusen
Germany

Dr. Hubert Mertens
PH-OP-QA Head of Integrated
Quality Management

Tel. +49 214 30 32997
Fax +49 214 30 50025
hubert.mertens@
bayerhealthcare.com
www.bayerhealthcare.com

Board of Management:
Wolfgang Plischke,
Chairman of the Board
Gunnar Riemann
Werner Baumann

Chairman of the
Supervisory Board.
Richard Pott

Registered Office:
Leverkusen
Local Court Köln
HRB 49894

Dear Madam, dear Sir,

Bayer HealthCare appreciates the opportunity to comment on the a.m.
FDA Draft Guidance. Please find in the following the general as well as
the specific comments.

General Comments:

1. The requirements for the quality of the drug substance are not aligned with the concept of „Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach“ of the FDA.
2. Several requirements are inconsistent with the worldwide accepted and established guideline ICH Q7A.
3. Starting materials for synthetic drug substances (Attachment 1): we recommend that this attachment should be revised focussing on a risk based and a science based approach. The presented API Starting Material (SM) concept is seen as an unjustified significant regulatory burden.

From our perspective in a scientific based approach an API SM should be defined at a step where it is in a balanced relationship to the synthetic generation of an API. An appropriate definition of the API SM should be developed in accordance with the existing ICH-requirements. In addition we recommend to follow the decision tree already published by PhRMA in Pharmaceutical Technology, February 2003. Key aspects in the definition

2003D-0571

C 5



Page 2 of 3

of an API SM should consider the following issues (instead of the criteria described in the draft guidance like propinquity, complexity of structure etc.):

- Significant structural fragment incorporated into the API structure
- specification is appropriate to ensure the quality and safety of API
- well characterized (not necessarily isolated and purified)
- appropriate analytical methodology / the use of advanced analytical techniques should be supported
- impact of API-SM quality on API quality is known and controlled (relevant is the question if an impurity is known, fully controlled and toxicologically qualified; it is not relevant if the API Starting Material or another intermediate is the origin of an impurity)
- purification sequence is part of the API synthesis. Process should be developed and optimized in order to guarantee adequate downstream purification.
- Stability is understood

Attachment I, Chapter II - Documentation: it should be revised and structured in accordance with chapter I under the consideration of the above mentioned key aspects.

We recommend an appropriate wording for Attachment I – Documentation, e.g.: “API Starting materials should be fully characterized to ascertain suitability for intended use, and the possibility of transferring impurities from the starting material to the final active substance should be discussed. For API SM complete specifications should be provided, including an impurity profile. Impurities present in a API SM may be carried through the synthesis/process unchanged or as derivatives, and should therefore be controlled in the API SM by appropriate acceptance criteria with suitably validated methods. Acceptance criteria should be established by the applicant based on evaluation of the fate of impurities present in the API SM, when subject to the normal synthesis/process. Acceptance criteria for accepting or rejecting batches should be indicated. The control of API-SMs should be designed to detect isomeric or other impurities which are potentially reactive and be carried through to the final product of the synthesis.



Page 3 of 3

The introduction of the new definition of a *starting material for application purposes* extends the detailed description of the manufacturing process in conjunction with the requirement for the commercial availability. This results in a significant increase in change control in the production although GMP is not required. The new criterion significant non-pharmaceutical market is in contradiction to the request for high purity of the material. The parameter "Propinquity" leads to the requirement of several reaction steps after the introduction of the API SM. This does not reflect to the risk of additional impurities related to the chemical reaction itself.

Specific Comments

Aside from the general comments the document would benefit from consideration of the specific comments listed in the separate table (see attachment).

Yours sincerely,

Dr. Hubert Mertens
PH-OP-QA-IQM

Dr. Oliver Brehm
PH-OP-CE/EA

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Specific Comments by Bayer HealthCare on FDA Draft Guidance on Drug Substance - CMC Doc. No. 2003D-0571, CDER 200389	Rationale	Importance 1= Major 2= Moderate 3=Minor
					1
363-365	II. C. (S.1.3)		<i>Detailed information on the characterizationof these and other physical forms and conditions required to produce one form or another - should be provided</i>	In many cases it might not be possible to produce every single modification in pure form due to e.g. hygroscopicity, instability etc. Studies to produce modifications can be reported.	2
377-393	IV.A (S.2.1)		<i>The name, address, and manufacturing responsibility should be provided for each firm (including contract manufacturers and testing laboratories) and each site when the application is submitted to FDA</i>	Detailed information requested concerning contract manufacturers, testing laboratories, manufacturing buildings, room numbers of processing areas should not be part of the CMC information, but presented during site inspection (see also information required in appendix X.A.1).	2
409-412	IV.B. (S.2.2)		<i>The entire manufacturing process should be depicted (i.e. API starting materials through drug substance release testing) . See Attachments 1 and 2 for information on API starting materials.</i>	For clarification please use the wording API starting material based on ICH Q7A.	1
488-489	IV.B.(S.2.2)		<i>A statement risk analysis should be provided that if bovine-derived materials from bovine spongiform encephalopathy (BSE) countries ... Are not used or manipulated in the same facility .</i>	The use of such materials in the same facility depends on various factors (as part of the risk analysis) like the source and kind of material, facility design, equipment, removal/inactivation steps, cleaning, cleaning validation data etc.	2
496-498	IV.B.(S.2.2)		<i>Significant Differences between the manufacturing process described in S.2.2. and the manufacturing process used to produce the primary stability batches should be discussed in S.2.6.</i>	Adaption to wording in line 908.	2
576-579	IV.B. (S.2.2)		<i>Repetition of a single reaction step should be carefully evaluated with respect to the potential formation of by-products and over-reacted materials . Repetition of multiple reaction steps is considered to be reworking , rather than reprocessing</i>	There is no rationale to limit reprocessing to only one reaction step	2

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Specific Comments by Bayer HealthCare on FDA Draft Guidance on Drug Substance - CMC Doc. No. 2003D-0571, CDER 200389	Rationale	Importance 1= Major 2= Moderate 3=Minor
688-695	IV.C.(S.2.3)		In general, the starting material and API starting material should be the same for a synthetic drug substance. However for a drug substance derived from biological source the starting material (e.g., plant) and API starting material (e.g., extract) can be different. In this case, information on the biological source (e.g. potential pathogens, herbicides, pesticides) is warranted in the applications so FDA can evaluate the suitability of the biological source as a starting material for drug substance (). The recommendations for starting materials provided in this guidance are for application purposes. See ICH Q7A for recommendations on API starting materials.	In general, in the total guidance it should be clarified if the term starting materials is used in the sense of ICH Q7A, i.e. API Starting materials, or in the sense of raw materials used for synthesis. The need to submit additional information on pathogens, herbicides or pesticides should be subject to a risk assessment.	1
697-698	IV.C.(S.2.3)		Starting materials for a synthetic drug substance are chemical compounds which are incorporated into the drug substance as important structural element of defined molecular structure that contribute to the structure of the drug substance.	It is essential only to reflect important structural elements rather than every single basic moiety	1
723-724	IV.C.(S.2.3)		The following information should be submitted in S.2.3 for reagents, solvents, and other auxiliary materials (e.g. filter aids, decolorizing agents) used in the manufacture of a drug substance :- in addition see line 721 und 731	The submission of a specification for auxiliary materials should be based on a sound evaluation regarding the criticality.	1
893-896	IV.F.(S.2.6)		The primary focus of this description should be the relationship between significant changes in the manufacturing process or manufacturing site and any associated changes in the chemical and physical properties of the drug substance.	Adaption to wording in line 908	2
1019-1020	V.B.(S.3.2)		Substances that are considered potential impurities but that have not been observed in the batches of drug substance manufactured	There is no need to discuss theoretical impurities never occurred during development. In addition even sound scientific considerations cannot ensure that all potential impurities are covered.	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Specific Comments by Bayer HealthCare on FDA Draft Guidance on Drug Substance - CMC Doc. No. 2003D-0571, CDER 200389	Rationale	Importance 1= Major 2= Moderate 3=Minor
1059-1060	V.B.(S.3.2)		Summary of the route of synthesis or method of preparation if the impurity or potential impurity was independently prepared.	Sentence does not make sense, preparation of impurities is usually performed in a lab. The quality of the standard is essential, not the manufacture.	1
1063-1064	V.B.(S.3.2)		A table listing the qualified level of expected impurities with a cross-reference to the appropriate studies (including study numbers and batch numbers).	Batch numbers are sufficient for correlation between API and study.	2
1086-1088	VI.A(S.4.1)		If the drug substance is processed (e.g. micronized) before it is used to manufacture the drug product, the specification for the unfinished drug substance if there is one should be included in section in S.2.4 . However based on manufacturing experience it might be appropriate to reduce testing of either the micronized or the non-micronized form.	Redundant testing on both forms does not enhance safety	1
1129	VI.A(S.4.1)		Add footnote: This is an example specification and is not intended to imply that these are typical tests and acceptance criteria for synthesized drug substances	Comparable to footnote in Table 2	3
1263-1264	VI.D(S.4.4)		The batch analysis reports should include results from all tests performed on the batch including tests that are not part of the according to the proposed specification	All parameters that are relevant should be included in the specification and only these should be reported.	2
1666-1989 and 1990-2106	attachment 1 and attachment 2		Delete complete attachment 1 and 2. Revise the attachments considering the criteria described in the general comment.	The new concept described in attachment 1 is in contrast to ICH Q7A and current industry practice (see PhRMA paper) and imposes major regulatory burden to the applicant without increasing quality and safety of APIs .	1